Preparation of *L*-Prolinamide Functionalized Mesoporous SBA-15 as Catalysts for Asymmetric Aldol Addition

Chieh Chien (簡婕) and Soofin Cheng (鄭淑芬)

Department of Chemistry, National Taiwan University
Email: r99223115@ntu.edu.tw

Abstract

L-prolinamide functionalized mesoporous SBA-15 materials were prepared from thiol group functionalized SBA-15 (SH-SBA-15), which was formed by one-pot co-condensation of TEOS and MPTMS using P123 copolymer as surfactant in strong acidic environment, and prolinamide through thiol-ene addition. XRD patterns showed that the materials contained well-ordered mesopores arranged in 2-D hexagonal arrays. N_2 sorption data showed that the surface area, pore volume, and pore diameter decreased after L-prolinamide was immobilized. Sulfur *K*-edge XANES spectra showed the existence of C-S-C bond. ^{13}C solid state NMR confirmed the presence of prolinamide structure. SEM and TEM images showed that the morphology and mesoporosity did not change after L-prolinamide immobilization. The immobilized catalysts were highly efficient in the asymmetric aldol reactions. The effects of solvents and different ketones reacting with *p*-nitrobenzaldehyde were examined.

Keywords: Mesoporous, Immobilized, Asymmetric, Aldol Reaction.

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1 Introduction

The asymmetric organocatalysis has become an important area of research in asymmetric catalysis. The direct asymmetric aldol reaction is an important method to form carbon-carbon bond, which provides directly access to the optically β-hydroxycarbonyl structure in many natural products and drugs.[1] Since List and co-workers [2] reported the aldol reaction catalyzed by proline in 2000, therehave rapid growth in the field of asymmetric reactions catalyzed by organocatalysts in the recent years, especially proline and its derivative, including prolinamides [3], prolinethiolmide [4], prolinesulfonamides [5] and so on. In this paper, the prolinamide catalyst is immobilized on mseoporous silica through covalent bonds. The immobilized prolinamide catalysts have the advantage of easy separation and reuse. Since the discovery of mesoporous silica M41S in 1992 [6], these materials with high surface areas (>1000 m^2/g), uniform pore sizes and high hydrothermal stability have been applied to adsorption, catalysis, electro-optical, and biomeducals. SBA-15 [7] which has larger pore size and higher hydrothermal stability than M41S series is used in the present study.

2 Experimental

2.1 Preparation of thiol group functionalized SBA-15 with different morphologies by co-condensation method

Conventional SBA-15 of rod-shape was prepared according to the procedure report in reference 8. 4.2 g of TEOS (Acros 98%) was added in a solution containing 2.00 g of Pluronic P123 triblock copolymer (Aldrich, Mn = 5800) and 80.0 g of 2 M HCl at 35℃ and pre-hydrolysis for 2 h. After adding mercaptopropylmethylsilane (MPTMS, Acros 98%) the mixture was sealed in a polypropylene bottle and kept stirring at 35 ℃ for 22 h, and then hydrothermally heated at 90 ℃ under static condition for another 24 h. The molar compositions of the reactants were P123: TEOS: HCl: H_2O = 0.017:1:7.94:221. The solid product was filtered, washed with deionized water, and dried at 50 ℃ overnight. The P123 templates were

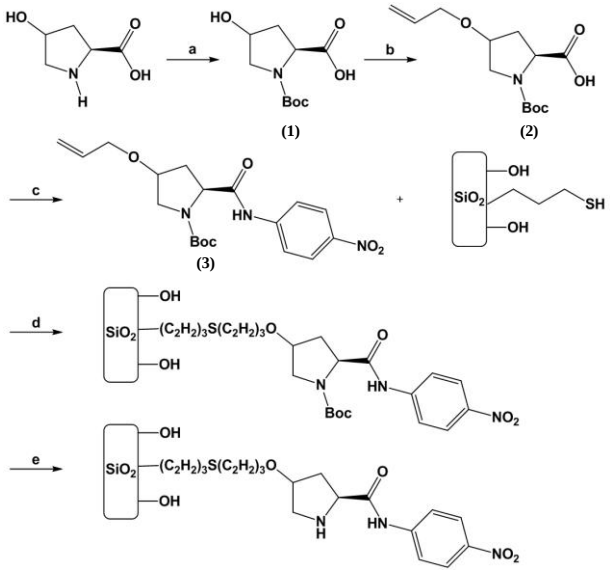
removed by ethanol extraction under reflux for 24h. The resultant material is designated SH-SBA15. Amorphous silica was also prepared by the same condition only without any template. The resultant material is designated SH-SiO_2. Platelet SBA-15 was prepared by adding a small amount of Zr (IV) ions in the conventional SBA-15 synthesis solution. The reactant compositions were P123: TEOS: $ZrOCl_2 \cdot 8H_2O$: HCl: H_2O = 0.017:1:0.05:7.94:221. The resultant material is designated SH-ZrSBA15. Platelet SBA-15 with expanded pore diameter was prepared by adding trimethylbenzene (TMB, Acros) after prehydrolysis of TEOS for 25 min in the platelet SBA-15 synthesis solution [9]. The resultant material is designated SH-ZrSBA15-TMB.

2.2 Synthesis of tert-butyl 2-(4-nitrophenylcarbamoyl) -4-(allyloxy) pyrrolidine-1-carboxylate (3)

As shown in Scheme 1, to a solution of *trans*-4-hydroxy-*L*-proline (11.5 g, 87.5 mmol) in 115 mL THF/H_2O (2/1 v/v), 40 mL of 10% (w/v) NaOH solution was added, followed by addition of di-t-butyl dicarbonate (23 g, 105 mmol) dropwise at 0℃. The reaction mixture was stirred at rt overnight, concentrated in vacuo, acidified with 10% (w/v) $KHSO_4$ solution, and extracted with ethyl acetate. The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the title compound **(1)**. To a suspension of NaH (2.1 g, 87.5 mmol) in dry THF (50 mL) cooled to 0℃ under nitrogen atmosphere was added a solution of (1) (8 g, 34.6 mmol) in THF (50 mL) dropwise. When the addition was complete, the mixture was allowed to come to rt and stir for 1 h. To the reaction mixture was then added allyl bromide (3.8 mL, 34.6 mmol) dropwise. The resulting mixture was stirred at rt overnight. The reaction was quenched by adding 2M HCl and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a clear, colorless oil **(2)**. A solution of DCC in THF (1.14 g, 5.5 mmol) was slowly added to a solution of **(2)** (1.5 g, 5.5 mmol) in THF and Stirred the reaction for half an hour. Then, added 4-nitroaniline (0.84 g, 6.05 mmol) and stirred at rt for 24 h. The byproduct N,N'-dicyclohexylurea were removed by filtration and the organic phase was concentrated in vacuo. Flash chromatography (silica gel, 20percent Hexane/ CH_2Cl_2) gave the tert-butyl 2-(4-nitrophenylcarbamoyl)-4-(allyloxy) pyrrolidine-1-carboxylate as a yellow solid. **(3)**

2.3 Immobilization of (3) onto SH-SBA15 via thiol-ene addition

SH-material was put in a two-neck bottle then under a reduced pressure. Appropriate amount of compound **(3)**, AIBN and 10 mL toluene were injected and reacted at 100℃ for 48 h. The solid was filtered, washed with ethanol, dried at 100℃. The tert-butoxycarbonyl group was removed by treatment with 10 mL CH_2Cl_2/TFA (4/1, v/v) solution, and reacted at rt for 6 h. The solid was filtered, and washed with ethanol, dried at 100℃. The catalysts were designated PLAM-SiO_2, PLAM-SBA15, PLAM-ZrSBA15 and PLAM-ZrSBA15-TMB.



Scheme 1: Reagents and conditions: (a) Boc_2O, NaOH, THF at rt; (b) allyl bromide, NaH, THF at rt; (c) *p*-nitroaniline, DCC, THF at rt; (d) AIBN refluxing in toluene; (e) TFA, DCM at rt, 6h.

2.4 Asymmetric aldol addition reaction

The PLAM-material, ketone and solvents were mixed in a flask and stirred for 30 min. After specific reaction, an aliquot (100 μL) of the reaction mixture was removed and diluted with EtOAc (1 mL), the solids were filtered by PVDF membrane, the filtrate was analyzed by HPLC equipped with a Daicel Chiralpak AD–H column under the separation condition of *i*PrOH/Hexane = 5/95, flow rate 1 mL/min, detection at λ= 254 nm.

3 Results and discussion

3.1 Structure characterization

The small angle powder XRD patterns of SH-materials and PLAM-materials are shown in Figure 1(a). All SBA-15 type samples show well-resolved diffraction peaks, which are indexed to the (100), (110), (200) diffractions of 2D-hexagonal *p6mm* mesostructure. The N_2 sorption isotherms show that all SBA-15 samples are type IV isotherms with H1 hysteresis loops at P/P_0 in the range of 0.45-0.80 (Figure 1(b)). The structural properties of SH-materials and PLAM-materials are summarized in Table 1. After covalently bonding prolinamide onto the surface of SH-materials, the surface area, pore volume, and pore diameter decrease.

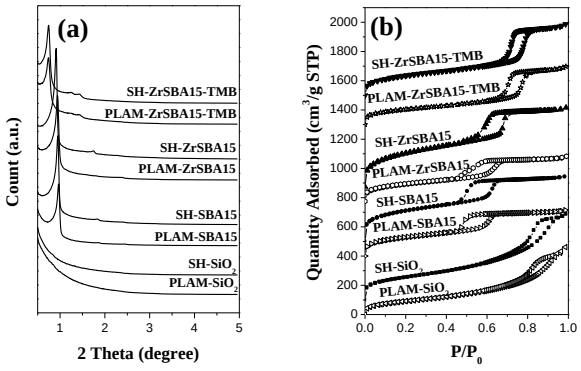


Figure 1: (a) Small-angle XRD patterns, (b) N_2 sorption isotherms of SH-materials and PLAM-materials.

Table 1: Physico-chemical properties of SH-materials and PLAM-materials.

Sample	a_0[a] (nm)	S_{BET} (m^2/g)	V_p (cm^3/g)	ϕ_{a_BdB} (nm)	ϕ_{d_BdB} (nm)	Catalyst content[b] (mmol/g)
SH-SiO_2	-	547	0.88	-	-	-
PLAM-SiO_2	-	339	0.71	-	-	0.57
SH-SBA15	11.9	729	0.68	5.1	4.9	-
PLAM-SBA15	11.6	458	0.47	5.0	4.8	0.61
SH-ZrSBA15	12.4	827	0.83	5.9	5.8	-
PLAM-ZrSBA15	12.2	422	0.45	5.5	5.5	0.63
SH-ZrSBA15-TMB	15.1	487	0.75	8.3	8.6	-
PLAM-ZrSBA15-TMB	15.3	370	0.61	8.1	8.1	0.52

[a] Unit cell parameter $a_0 = 2d_{100}/\sqrt{3}$.
[b] Measured from elemental analysis.

SEM and TEM images supply the direct evidences of the platelet morphology and 2-D hexagonal porosity (Figure 2). Sulfur *K*-edge XANES spectra shown in Figure 3(a) confirm the C-S-C bonding with the absorption appears at 2472 eV. Solid state ^{13}C CP/MAS NMR spectra of PLAM-materials are shown in Figure 3(b), and prove the incorporation of prolinamide group.

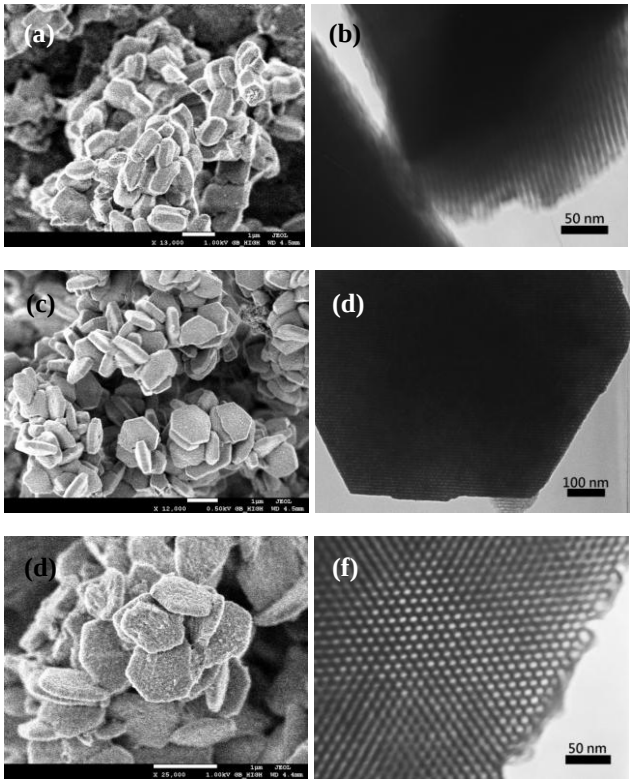


Figure 2: SEM and TEM images of synthesized catalysts. (a)(b)PLAM-SBA15, (c)(d)PLAM-ZrSBA15, (e)(f)PLAM-ZrSBA15-TMB.

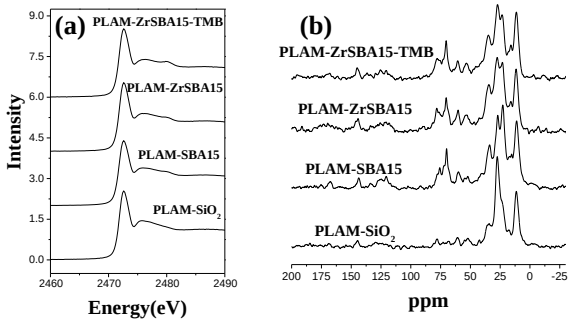


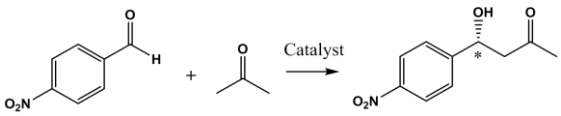
Figure 3: (a) Sulfur K-edge XANES spectra, (b) ^{13}C CP/MAS NMR spectra of PLAM-materials.

3.2 Catalytic performance of prolinamide functionalized mesoporous materials

The solvent was found to play an important role in the

catalytic performance of the materials (Table 2) in asymmetric aldol addition reaction of *p*-nitrobenzaldehyde and acetone (Scheme 2). The reaction did not proceed in apolar solvents (dichloromethane and hexane). The conversions were significantly increased by using polar solvents. Moreover, solvents of medium dielectric constants, such as EtOH and DMSO, gave the highest enatioselectivity.

In asymmetric aldol addition reaction of *p*-nitrobenzaldehyde and cyclohexanone (Scheme 3), water gave the highest conversion and enatioselectivity among the solvents studied (Table 3). It was proposed that the reactants which were insoluble in water might be concentrated around the catalytic sites [10]. The cage effect of water in asymmetric aldol addition of *p*-nitrobenzaldehyde and acetone was less significantly, because acetone is soluble in water.

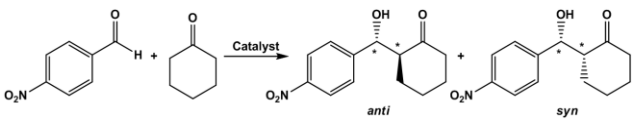


Scheme 2: Intermolecular asymmetric aldol reaction of p-nitrobenzaldehyde with acetone

Table 2: Solvent effect on asymmetric aldol reaction of p-nitrobenzaldehyde with acetone[a].

Entry	Solvent	Conversion[b] (%)	ee[b] (%)
1	acetone	22	35
2	CH_2Cl_2	<1	42
3	Hexane	<1	28
4	EtOH	17	40
5	DMSO	20	48
6	H_2O	13	26

[a] Reaction conditions: *p*-nitrobenzylaldehyd (0.23 mmol), acetone (0.5 mL), solvent (1.5 mL), catalyst 50 mg (10PLAM-ZrSBA15), 25 ^{0}C, 24 h.
[b] Enantiomertic excess determined by chiral HPLC.



Scheme 3: Intermolecular asymmetric aldol reaction of p-nitrobenzaldehyde with cyclohexanone.

Table 3: Solvent effect on asymmetric aldol reaction of p-nitrobenzaldehyde with cyclohexanone [a].

Entry	Solvent	Conversion[b] (%)	syn:anti[c]	ee[b] (%)
1	Cyclohexanone	21	23:77	88
2	CH_2Cl_2	4	16:84	77
3	Hexane	3	11:89.	73
4	EtOH	23	12:88	87
5	DMSO	25	8:92	90
6	H_2O	52	7:93	92

[a] Reaction conditions: *p*-nitrobenzylaldehyd (0.23 mmol), cyclohexanone (0.5 mL), solvent (1.5 mL), catalyst 50 mg (10PLAM-ZrSBA15), 25 ^{0}C, 24 h.
[b] Enantiomertic excess determined by chiral HPLC for *anti*-isomer.
[c] Diastereomeric excess determined by ^{1}H NMR.

Table 4 shows the effect of cyclohexanone / water ratio on asymmetric aldol reaction of *p*-nitrobenzaldehyde and cyclohexanone. The conversion increased with the decrease in cyclohexanone to water ratio. The slight lower conversion observed in Entry 1 with the lowest cyclohexanone/ water ratio about 1/6 may be due to inhomogeneous mixing .

The effect of post-treating PLAM-materials with ethanol to remove P123 residue prior to anchoring prolinamide derivative on the catalytic activities are shown in Figure 4.

Table 4: The effect of cyclohexanone / water ratio on asymmetric aldol reaction[a].

Entry	Ketone/H_2O	Conversion[b] (%)	syn:anti[c]	ee[b] (%)
1	1/6	72	8:92	91
2	1/5	77	7:93	91
3	1/4	68	7:93.	92
4	1/3	52	7:93	92
5	1/1	48	9:91	92
6	3/1	40	9:91	91

[a] Reaction conditions: *p*-nitrobenzylaldehyd (0.23 mmol), the total volume of cyclohexanone and water is 2 mL, catalyst (10PLAM-ZrSBA15) 50 mg, 25 ^{0}C, 24 h.
[b] Enantiomertic excess determined by chiral HPLC for *anti*-isomer.
[C] Diastereomeric excess determined by 1H NMR.

In comparison to the materials without ethanol treatment, the *p*-nitrobenzaldehyde conversion increases from 57% to 77% in 12 h and to 93% in 24 h (Figure 4), during the asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde.

The effect of mesostructure on the molecular diffusion during the heterogeneous catalytic reaction was studied. All prolinamide functionalized mesoporous SBA-15 or amorphous silica materials showed catalytic activity and enantioselectivity in asymmetric aldol reaction of

p-nitrobenzaldehyde with cyclohexanone (Figure 5). Rod-like PLAM-SBA15 gave the highest activity but lower ee value. Platelet like PLAM-ZrSBA15 and pore expanding PLAM-ZrSBA15-TMB show the similar conversion for p-nitrobenzaldehyde in 24 hours (Table 5) and the higher enantioselectivity (91% ee for the major anti-isomer). Amorphous silica PLAM-SiO_2 shows the lowest activity and ee value. The results demonstrateed that the highly ordered mesopores played an important role in the catalytic performance and the platelet like materials with large pore size exhibited the highest enantioselectivity.

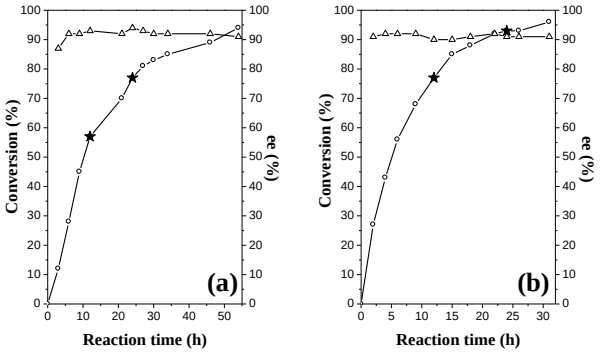


Figure 4: Effect of (a) before and (b) after post-treatment with ethanol on the catalytic performance.

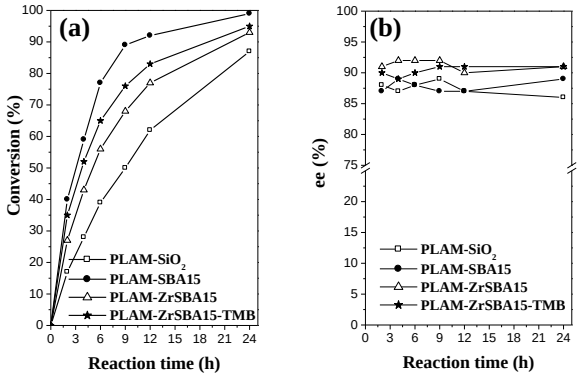


Figure 5: The catalytic performances (a) conversion and (b) enantioselective of PLAM-materials over PLAM-SBA15 with various morphologies and and mesoporosities.

Table 5: Catalytic performance of PLAM-silica materials with various morphologies and mesoporosities.

Entry	Catalyst	Shape	Conv[b] (%)	syn:anti[c]	ee[b] (%)
1	PLAM-SiO_2	irr	86	8:92	86
2	PLAM-SBA15	Rod	99	8:92	89
3	PLAM-ZrSBA15	Plate	93	7:93	91
4	PLAM-ZrSBA15-TMB	plate	95	7:93	91

[a] Reaction conditions: *p*-nitrobenzylaldehyd (0.23 mmol), cyclohexanone (0.33mL), solvent (1.67mL), catalyst 50mg, 25^0C, 24h.
[b] Enantiomertic excess determined by chiral HPLC for *anti*-isomer.
[c] Diastereomeric excess determined by ^{1}H NMR.

4 Conclusions

L-Prolinamide functionalized mesoporous SBA-15 catalysts with different morphologies and pore sizes have been successfully synthesized. The 2-D hexagonal pore arrangement and morphology were maintained after N-Boc-4-O-allyl-hydroxyprolinamide was immobilized on mesoporous SBA-15. The immobilized *L*-Prolinamide showed excellent catalytic activities in asymmetric aldol reactions. Among the various solvents used in the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde, water gave the highest conversion and e.e. selectivity. The highly ordered mesopores played an important role in the catalytic performance.

Acknowledgments

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